Section of Odontology

President J Boyes FRCSED FDS RCS

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Papers

Autoimmunity in Oral Diseases, with Special Reference to Recurrent Oral Ulceration

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Autoimmunity can be defined as the damage produced by the action of humoral or cell-bound antibodies, stimulated by normal components of the body. This concept admits the possibility that antibodies can be stimulated not only by foreign substances, e.g. bacteria, but also by the body's own substances or 'self-antigens'. It is, of course, a bold departure from the classical notion that antibodies are stimulated by micro-organisms in order to protect the body from infection. Indeed, the exclusive defensive role of antibodies has been changed into an offensive role. What precipitates this loss of tolerance to one's own tissue is not understood. However, once tolerance to self-antigens is broken, auto-antibody formation may occur.

At least four possible mechanisms of auto-antibody stimulation have been postulated:

(1) Segregated antigen released by trauma, infection or other pathogenic agents into the reticulo-endothelial system may be treated as a 'foreign' antigen and produce antibodies, e.g. lens protein and thyroglobulin.
(2) Pathological tissue alteration may induce formation of antibodies to tissues which are normally non-antigenic; these antibodies are capable of cross-reacting with similar antigenic determinants in the normal tissue, e.g. cardiac infarction and hepatic necrosis.
(3) Hapten-protein formation may result from the combination of drugs or chemicals with a normal tissue protein component and induce antibody formation to that protein, e.g. apronal (Sedormid) purpura.
(4) Antigenic cross-reactivity between micro-organisms and some tissue component may lead to the formation of auto-antibodies, e.g. β-hæmolytic streptococci and heart tissue, *Escherichia coli* and colonic mucosa.

Table 1
Characteristic features of autoimmunity
(Mackay & Burnet 1963)

(1) Raised γ globulin
(2) Presence of autoantibodies
(3) Deposition of altered globulin in the lesion
(4) Mononuclear infiltration of the lesion
(5) Association with other immunological diseases
(6) Favourable response to steroids

Table 2
Criteria for autoimmune pathogenesis
(Witebsky 1959)

(1) Specific humoral or cell-bound antibodies should be demonstrated
(2) The antigen should be identified and should induce humoral or cell-bound antibodies in animals
(3) Antigenic stimulation of the animal should lead to the disease
(4) The experimental disease should be capable of passive transfer with serum or cells

The characteristic markers of autoimmune disorders were described by Mackay & Burnet in 1963 (Table 1), although the presence of these features is no proof of autoimmunity. In order to accept that an autoimmune pathogenesis is responsible for a particular disease, Witebsky (1959) postulated the equivalent of Koch's postulates (Table 2).

Immunological disorders may affect the mouth in four ways (Table 3). The classification is necessarily tentative, as our knowledge of some of these

Table 3
Immunological disorders of the mouth

Autoimmune conditions of oral tissues
Sjögren's syndrome
Rheumatoid arthritis
Lupus erythematosus
Myasthenia gravis
Pemphigus
Recurrent aphthous ulcers
Oral manifestations of autoimmune disease
Pernicious and idiopathic hæmolytic anæmia
Idiopathic Addison's disease
Idiopathic thrombocytopenic purpura
Endocrine-candidosis syndrome
Lesions with abnormal immune manifestations
Wegener's granulomatosis and polyarteritis
Scleroderma
Focal sepsis
Immunoglobulin abnormalities
Agammaglobulinæmia
Myelomatosis, Macroglobulinæmia } Amyloidosis

diseases is limited. It is nevertheless revealing to note the large number of immune disorders involving oral tissues. Only the first two groups show autoimmune manifestations, so that the discussion will be limited to them.

Autoimmune conditions of oral tissues may involve: the salivary glands in Sjögren's syndrome; bone and joints in rheumatoid arthritis; mucosa in lupus erythematosus, pemphigus and recurrent aphthous ulcers; muscles in myasthenia gravis. There is considerable evidence in favour of an autoimmune pathogenesis in Sjögren's syndrome (Bunim 1961), rheumatoid arthritis and systemic lupus erythematosus (Glynn & Holborow 1965).

Table 4
Three varieties of focal recurrent oral ulcers

	Minor aphthous ulcers (MiAU)	*Major aphthous ulcers (MjAU)*	*Herpetiform ulcers (HU)*
Sex ratio F:M	1·3:1	0·8:1	2·6:1
Age of onset (peak incidence)	10–19 years	10–19 years	20–29 years
Number of ulcers	1–5	1–10	10–100
Size	<10 mm	>10 mm	1–2 mm
Duration	4–14 days	10–30 days	7–14 days
Healing by scar	8%	64%	32%
Recurrence	1–4 months	<monthly	<monthly
Sites	Lips, cheeks, tongue	Lips, cheeks, tongue, pharynx, palate	Lips, cheeks, tongue, pharynx, palate, floor, gum
Total duration	<5 years	>15 years	<5 years
Associated oral lesions	—	Erythema migrans	—
Treatment	Corticosteroids	Corticosteroids	Tetracycline
Immunoglobulins	Raised IgG, IgA	Raised IgG, IgA	Raised IgA
Humoral antibodies	Raised	Raised	—
Cell-bound antibodies	Present	Present	±
Intra-epithelial vesicles and inclusion bodies	—	—	Present

However, in pemphigus (Beutner & Jordon 1964) and myasthenia gravis (Beutner *et al.* 1962) the evidence is incomplete and recurrent aphthous ulcers will be fully discussed.

Oral manifestations of autoimmune disease include a number of endocrine, hæmatological and gastric conditions in which the lesions are thought to be due to autoimmune disorders, the oral manifestations being a remote effect of the pathological lesion. Patients with pernicious anæmia and less commonly hæmolytic anæmia may present with a sore atrophic tongue or difficulties in surgical and prosthetic management. Patients with Addison's disease often show oral pigmentation and those with thrombocytopenic purpura may display gingival and surgical bleeding. Children with idiopathic parathyroid and adrenal deficiency often show chronic hyperplastic candidosis.

RECURRENT ORAL ULCERATION

This is the most common disease affecting the oral mucosa. It must be differentiated into three conditions as these show distinct clinical, pathological and immunological characteristics. The terminology followed will be that introduced by Truelove & Morris-Owen (1958), whereby recurrent aphthous ulcers (RAU) are divided into minor and major varieties. Evidence will be presented to support the view that major aphthous ulcers (MjAU) are more severe variants of minor aphthous ulcers (MiAU). The term periadenitis mucosa necrotica recurrens is a misnomer and will be substituted by MjAU. The third type of ulcers will be referred to as herpetiform ulcers (HU) (Cooke 1960). The clinical manifestations of recurrent oral ulcers have been particularly well documented by Sircus *et al.* (1957), Farmer (1958), Cooke (1961) and Ship *et al.* (1960). This paper deals predominantly with the differential diagnosis, and incidence of the three types of recurrent oral ulcers (Table 4), and the relationship of humoral antibodies to clinical features. Some aspects of recurrent oral ulceration in Behçet's syndrome will also be considered.

Table 5
Classification of 210 (and the first 100) patients with recurrent oral ulcers

	First 100 patients	*Total analysis of 210 patients*				
Group	*No. or %*	*No.*	*%*	*Males*	*Females*	*F:M*
MiAU	81	133	63	58	75	1·3:1
MjAU	8	25	12	14	11	0·8:1
HU	8	19	9	5	14	2·8:1
Behçet's syndrome	3	33	16	12	21	1·8:1
Total	100	210		89	121	1·4:1

Epidemiology

Two hundred and ten patients with recurrent oral ulcers were studied in this series and all but 9 of them were seen personally. Many of these patients were followed up for a period of up to four years and the collected clinical, and immunological data were recorded on a punch card system (Cope-Chat Paramount Sorting System) and then assessed and correlated statistically.

The incidence of the four groups of ulcers is shown in Table 5. Probably only the first 100 patients are representative of a population attending a department of oral medicine, as special problems were later more frequently referred to the department.

Sex (Table 5): A significant difference between the proportion of male and female patients among the four disease groups was not established ($\chi^2=4{\cdot}48$, d.f.3).

This also applies when a direct comparison is made between MiAU and MjAU ($\chi^2=1{\cdot}3$, d.f.1, $P>0{\cdot}05$) and between MiAU and HU ($\chi^2=2{\cdot}05$, d.f.1, $P>0{\cdot}05$). Nevertheless, the incidence in MiAU, MjAU and HU was slightly higher for females than males (1·27:1), though patients with MjAU showed a reversed ratio (0·8:1).

The herpetiform group of patients showed a considerably higher proportion of females.

Age at attendance (Figs 1–4): Analysis of the four groups by the χ^2 test failed to establish a significant difference between them in age groups less than 20 years, 20–39 years and greater than 39 years.

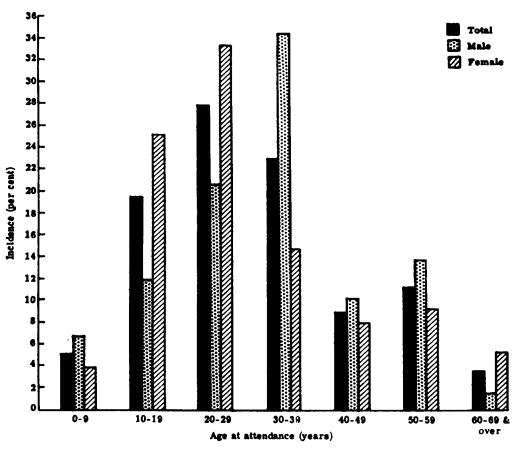

Fig 1 *Age at attendance of patients with minor aphthous ulcers*

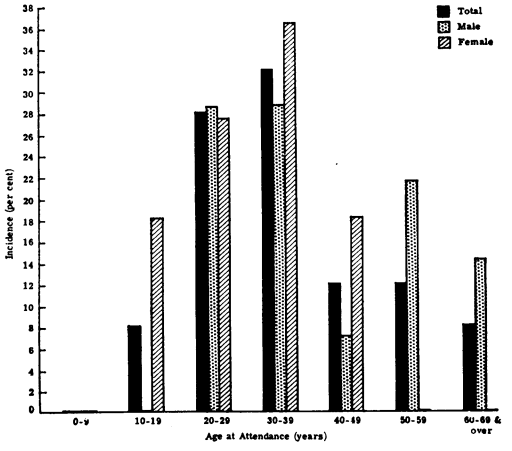

Fig 2 *Age at attendance of patients with major aphthous ulcers*

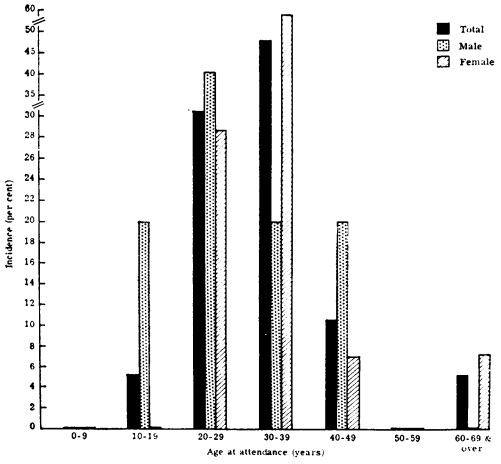

Fig 3 *Age at attendance of patients with herpetiform ulcers*

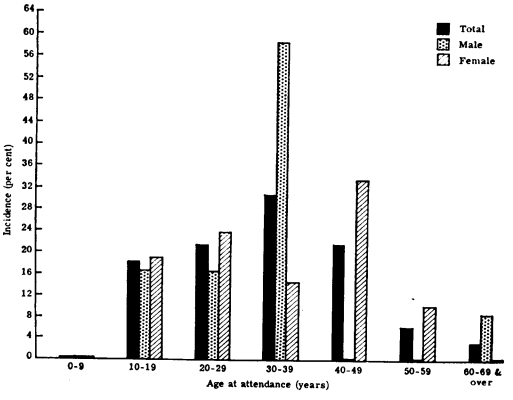

Fig 4 *Age at attendance of patients with Behçet's syndrome*

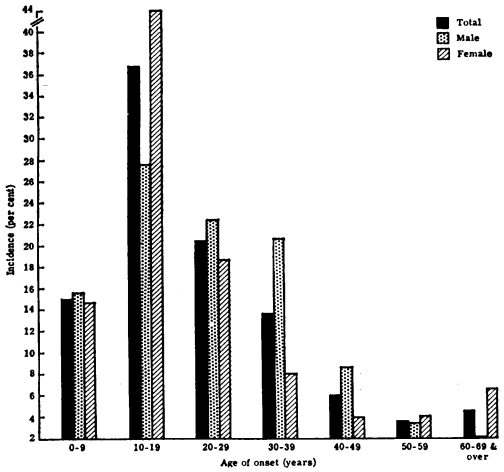

Fig 5 *Age of onset in patients with minor aphthous ulcers*

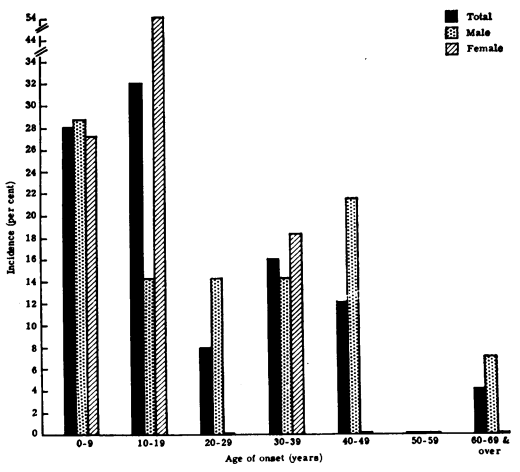

Fig 6 *Age of onset in patients with major aphthous ulcers*

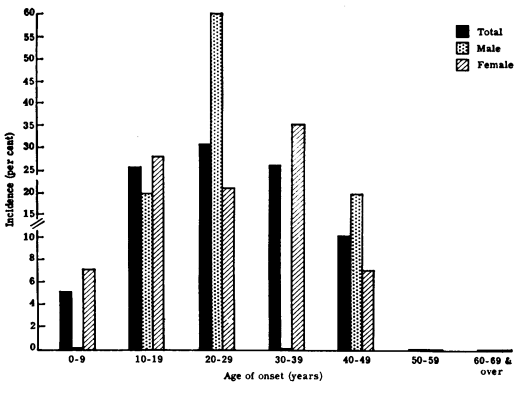

Fig 7 *Age of onset in patients with herpetiform ulcers*

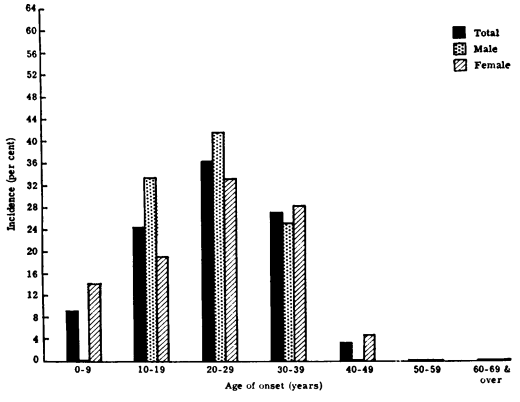

Fig 8 *Age of onset in patients with Behçet's syndrome*

Age of onset (Figs 5–8): A significant difference was established among the four groups between the proportion of patients with onset of ulceration before and after the age of 20 years ($\chi^2=6{\cdot}18$, d.f.3, $P<0{\cdot}05$). Ulceration started by the age of 39 years in 84–97% of all four groups. Maximum incidence of onset was 10–19 years in all patients with MiAU and females with MjAU, but 0–9 years in males with MjAU. However, in both sexes with Behçet's syndrome and males with HU, the peak onset of ulceration was 20–29 years but 30–39 years in females with HU.

The group of patients with the age of onset at 10–19 years was divided into males and females with ulcers starting at 10–14 years and 15–19 years, in order to find out if puberty might be involved in the onset of ulceration. The number of patients in these categories with MjAU, HU and Behçet's syndrome were too small for analysis. However, Fisher's exact test was applied to MiAU comparing 32 males and females with onset of ulceration at 10–14 years, with that of 17 patients at 15–19 years; a significant difference between the sexes was not established.

These data suggest that ulceration starts in the great majority of patients by the age of 40 years. It is unlikely that the four lesions belong to the same population since a significant difference was established between the patients with ulcers beginning before and after 20 years. A significant increase of onset of ulceration during puberty was not found.

Total duration of ulceration (Fig 9): A highly significant difference was found among the four groups between the proportion of patients with

duration of ulceration up to five years and greater than five years ($\chi^2=14{\cdot}0$, d.f.3, $P<0{\cdot}001$). A similar difference was detected between MiAU and MjAU ($\chi^2=13{\cdot}02$, d.f.l, $P<0{\cdot}001$), but not between MiAU and HU ($\chi^2=0{\cdot}09$, d.f.1).

The highest incidence of ulceration lasting over fifteen years was present in male patients with MjAU (64%) and that lasting up to five years in males with herpetiform ulcers (60%). Generally the duration of ulceration was longer in patients with MjAU and Behçet's syndrome and shorter in MiAU and HU.

Severity of ulceration (*Table 6*): The four groups could not be compared separately since the number of patients with mild ulcers was too small (4/68) in all except MiAU. The latter was therefore compared with the other three groups combined. MiAU was found to have a significantly higher proportion of mild cases ($\chi^2=23{\cdot}1$, d.f.1, $P<0{\cdot}001$; using Yate's correction). Direct comparison between MiAU and MjAU showed that the former has a very significant proportion of mild ulcers ($\chi^2=11{\cdot}63$, d.f.1, $P<0{\cdot}001$).

Clinical severity in terms of age of onset: Clinical severity was not related to the age of onset. MiAU was the only disease in which there were many patients with mild lesions (39%) and these were evenly distributed throughout the age groups.

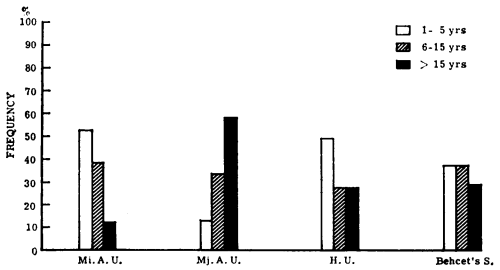

Fig 9 *Duration of ulceration*

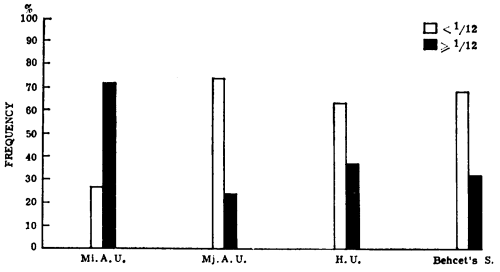

Fig 10 *Frequency of recurrences*

Frequency of recurrence (*Fig 10*): The proportion of patients with frequency of recurrence less than a month and a month or more showed highly significant differences in the four groups ($\chi^2=30{\cdot}7$, d.f.3, $P<0{\cdot}001$). Direct comparison showed a very highly significant difference between MiAU and MjAU ($\chi^2=18{\cdot}10$, d.f.l, $P<0{\cdot}001$) and a highly significant difference between MiAU and HU ($\chi^2=9{\cdot}50$, d.f.1, $P<0{\cdot}01$). A greater proportion of MiAU recur at monthly or longer intervals than MjAU or HU.

Table 6
Severity of ulceration

	Percentage of patients					
	Total		*Males*		*Females*	
	Mild	*Severe*	*Mild*	*Severe*	*Mild*	*Severe*
MiAU	39	61	41	59	37	63
MjAU	4	96	0	100	9	91
HU	11	89	0	100	14	86
Behçet's syndrome	8	92	10	90	7	93

There was little difference between the sexes in the frequency of monthly recurrences; 26% among male and 32% among female patients with MiAU. All female patients with MjAU and males with HU showed recurrences of up to one month's duration.

Table 7
Duration of episodes of ulceration

	Percentage of patients								
	<1 week			*1–2 weeks*			*>2 weeks*		
	T	*M*	*F*	*T*	*M*	*F*	*T*	*M*	*F*
MiAU	13	15	12	77	77	77	10	8	10
MjAU	0	0	0	72	64	82	28	36	18
HU	5	0	7	73	80	71	21	20	21
Behçet's syndrome	4	0	7	68	80	60	28	20	33

T, total. M, males. F, females

Duration of episodes of ulceration (*Table 7*): A significant difference was found among the four groups between patients with ulcers lasting up to two weeks and those over two weeks ($\chi^2=9{\cdot}60$, d.f.3, $P<0{\cdot}05$). This difference was also significant when MiAU were compared with MjAU ($\chi^2=4{\cdot}78$, d.f.1, $P<0{\cdot}05$) but was not significant when MiAU were compared with HU ($\chi^2=1{\cdot}15$, d.f.1).

Table 7 shows that 68–77% of ulcers from all four groups lasted 1–2 weeks. The highest incidence of ulcers lasting more than two weeks was among male patients with MjAU (36%) and females with Behçet's syndrome (33%). There was little difference in the duration of ulceration between the sexes at various ages.

Number of ulcers (*Fig 11*): The proportion of patients among the four groups having 1–4 and more than 4 ulcers was highly significant (χ^2= 68·4, d.f.3, P<0·001). A significant difference was established when 1–4 ulcers were compared with 5–10 ulcers in MiAU and MjAU (χ^2=5·49, d.f.1, P<0·05) and the difference was very significant when 5–10 ulcers were compared with 11–100 ulcers in MiAU and HU (P<0·001 by Fisher's exact test).

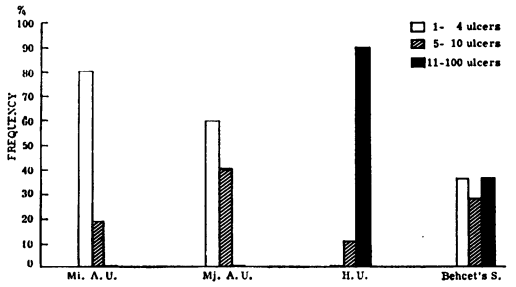

Fig 11 *Number of ulcers*

There is a gradual increase in the number of ulcers from MiAU to HU; more than 4 ulcers are present in 18% of MiAU, 40% of MjAU, 64% of Behçet's syndrome and 100% of herpetiform ulcers. The only difference between the sexes was seen in Behçet's syndrome with 60% of males and only 20% of females showing 1–4 ulcers. Most patients with MiAU have 1–4, MjAU 2–10 and HU 10–100 ulcers.

Size of ulcers (*Fig 12*): A very highly significant difference was found among the four groups when ulcers up to 10 mm were compared with those over 10 mm in size (χ^2=69·0 d.f.3, P<0·001). This applied also when MiAU were compared directly with MjAU (χ^2=70·51, d.f.1, P<0·001). Furthermore, a significant difference was found between MiAU and HU, comparing ulcers up to 2 mm with those greater than 2 mm in size (χ^2=12·01, d.f.1, P<0·01).

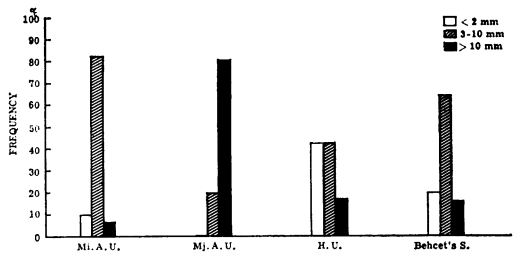

Fig 12 *Size of ulcers*

The herpetiform group had the largest proportion of small ulcers (42%) and the proportion would be greatly increased if the lesions were graded at the initial stages of ulceration before they coalesced into larger ones. MjAU group had the highest frequency of largest ulcers (80%). Most of the MiAU (83%) and Behçet's syndrome ulcers (64%) were 3–10 mm in size. The size of ulcers showed no marked variation with age and sex. An important difference in the mode of enlargement of ulcers is that in MiAU and MjAU an ulcer gradually increases in size, whilst in herpetiform lesions a number of small ulcers coalesce to form a larger lesion.

Sites of ulceration (*Table 8*): Lips and cheeks were affected in 82–100% of all patients without any appreciable differences among the sexes. A progressively rising incidence of involvement of the tongue was found; 52% in MiAU, 68% in MjAU, 80% in herpetiform ulcers and 88% in Behçet's syndrome. Pharyngeal involvement showed highly significant association with MjAU when compared with MiAU (χ^2=70·51, d.f.1, P<0·001) and the difference was very significant when HU was compared with MiAU (χ^2=12·01, d.f.1, P<0·01). The palate was also affected significantly in MjAU (χ^2=6·42, d.f.1, P<0·05) and highly significantly in HU (χ^2=33·61, d.f.1, P<0·001), when compared with MiAU. Involvement of gum (P<0·001 by Fisher's exact test) and floor of the mouth (χ^2=10·41, d.f.1, P<0·01) was significantly associated only in HU.

Table 8
Sites of ulcers

	Percentage of patients with involvement of						
	Lips	*Cheeks*	*Tongue*	*Floor*	*Palate*	*Gum*	*Pharynx*
MiAU	89	82	52	8	2	1	4
MjAU	100	84	68	16	16●	4	40●
HU	89	89	80	37●	42●	26●	42●
Behçet's syndrome	92	100	88	12	40	24	32

●P<0·05 or beyond

In Behçet's syndrome ulcers were found to involve the palate in 40%, pharynx in 32% and gum in 24% of patients. More females than males showed pharyngeal involvement in Behçet's syndrome and MjAU and gum involvement in HU.

It is evident that except for the lips and cheeks, there are differences in the sites of ulceration between the various groups of patients. A progressively rising frequency can be seen from MiAU to MjAU, Behçet's syndrome and HU in the involvement of the tongue, floor, palate, gum and pharynx. Hence the difference is most striking when MiAU is compared with HU.

Scarring (Table 9): Healing of ulcers with clinical scar formation probably depends on the extent of the lesion and the degree of secondary infection. There is a highly significant difference in the incidence of scarring when MiAU is compared with MjAU ($\chi^2=42{\cdot}28$, d.f.1, $P<0{\cdot}001$)). In Behçet's syndrome scars are not uncommon (24%) but a surprising feature was the presence of scars in HU in 32% of all patients and, indeed, in 60% of males. The difference in incidence of scarring between MiAU and HU was significant ($\chi^2=10{\cdot}41$, d.f.1, $P<0{\cdot}01$).

Most of the scars were initially stellar, but in a few patients with MjAU the scars were more extensive and tethered down, producing a puckering effect of the mucosa. The high incidence and often greater severity of scarring in MjAU makes this a useful feature in differential diagnosis from other lesions.

Table 9
Incidence of scarring

	Total		*Males*		*Females*	
	No.	*%*	*No.*	*%*	*No.*	*%*
MiAU	11/133	8	6/58	10	5/75	7
MjAU	16/25	64	9/14	64	7/11	64
HU	7/19	32	3/5	60	4/14	28
Behçet's syndrome	6/25	24	2/10	20	4/15	33

Table 10
Associated general and oral diseases

	No. of patients with		
General Disease	*MiAU*	*MjAU*	*HU*
Infantile eczema, asthma, or allergic conditions	7	0	1
Ulcerative colitis	5	0	1
Rheumatoid arthritis	2	0	0
Migraine	2	1	0
Renal disease	2	0	0
Peptic ulcer	0	0	2
Cœliac disease	1	0	0
Tuberculosis	1	1	0
Total	20	2	4
Percentage involvement	15%	8%	21%
Oral disease			
Erythema migrans linguæ	1	5	1
Chronic candidosis	4	2	0
Herpes labialis	2	0	0
Lichen planus	2	0	0
Smoker's keratosis	1	0	0
Vincent's gingivitis	1	0	0
Total	11	7	1
Percentage involvement	8%	28%	5·2%
Percentage involvement of general and oral diseases	23%	36%	26%

Table 12
Relation between complement-fixation test, precipitation test and sex incidence

	Positive complement-fixation test				*Positive precipitation test*			
	Males		*Females*		*Males*		*Females*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No*	*%*
MiAU	16/31	52	19/45	42	17/28	61	21/42	50
MjAU	5/8	62	4/6	67	6/10	60	2/7	28
HU	1/5	20	2/9	22	1/5	20	3/11	27
Behçet's syndrome	8/12	67	11/16	69	7/12	58	10/16	62

Associated diseases (Table 10): A variety of general and local diseases were found in 23% of MiAU, 36% of MjAU and 26% of herpetiform ulceration. Of the general conditions only ulcerative colitis (6 patients) and infantile eczema, asthma or allergic conditions (8 patients) were found in any number. Among the oral lesions only erythema migrans linguæ needs to be mentioned for the high incidence (20%) in MjAU; its presence was highly significant in MjAU as compared with MiAU ($P<0{\cdot}001$, by Fisher's exact test).

Correlation of Humoral Antibodies with Clinical Features

The use of fœtal oral mucosa as the antigen in the hæmagglutination, complement fixation and precipitation tests, as well as the results of these tests were reported previously (Lehner 1964, 1967*a*). In this study an attempt was made to correlate humoral antibodies with the clinical features in recurrent oral ulcers.

Sex (Tables 11 and 12): Analysis of hæmagglutination titres greater than 1:40 between males and females failed to show a significant difference between the sexes (MiAU, $\chi^2=1{\cdot}15$, d.f.1; MjAU, $P>0{\cdot}05$ and Behçet's syndrome $P>0{\cdot}05$ by Fisher's exact test). However, there was a tendency for male patients to yield a greater proportion of high titres (1:320–1:640). Complement fixation and precipitation tests also showed little difference between the sexes.

Table 11
Relation between hæmagglutination titre and sex

	Titre 0–1:40				*Titre 1:80–1:160*				*Titre 1:320–1:640*			
	Males		*Females*		*Males*		*Females*		*Males*		*Females*	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
MiAU	8/39	20	18/55	33	18/39	46	24/55	44	13/39	33	13/55	24
MjAU	3/12	25	2/11	18	5/12	42	8/11	73	4/12	33	1/11	9
HU	4/5	80	8/10	80	1/5	20	2/10	20	0	0	0	0
Behçet's syndrome	2/12	17	5/20	25	3/12	25	7/20	35	7/12	58	8/20	40

Table 13
Correlation of humoral antibodies and clinical features in minor aphthous ulcers (percent)

	No. tested	*Hæmagglutination titre* 0–1:40	1:80–1:160	1:320–1:640	*No. tested*	*Precipitation test* +	−	*No. tested*	*Complement-fixation test* +	−
Severity of ulcer										
Mild	30	37	40	23	19	42	58	26	38	62
Severe	64	23	47	30	51	59	41	58	53	47
Duration of ulcers										
≤5 years	46	33	48	20	32	44	56	41	54	46
>5 years	48	23	42	35	38	65	35	43	44	56

Age (Fig 13): Significant antibody levels are found at all ages.

Duration of ulceration (Table 13): Only the results of MiAU will be analysed here, since the number of patients with mild ulcers and a duration of less than 5 years is very small in the other 3 groups. In MiAU the duration of ulceration and the presence of a significant hæmagglutination titre are not correlated statistically; this applies to titres of 0–1:40, 1:80–1:160 and 1:320–1:640 ($\chi^2=223$, d.f.2), and to titres >1:40 ($\chi^2=0{\cdot}67$, d.f.1). The duration of ulceration does not influence the presence of complement-fixing antibodies, for the proportion in the shorter and longer than five-year groups is similar. However, the incidence of precipitating antibodies differs in the two groups; 44% when less than five years and 65% when greater than five years.

Severity of ulceration (Table 13): Comparison between sera from patients with mild and severe ulcers failed to show a significant difference in hæmagglutination titres of 0–1:40, 1:80–1:160 and 1:320–1:640 ($\chi^2=1{\cdot}81$, d.f.2), or of levels >1:40 ($\chi^2=1{\cdot}19$, d.f.1).

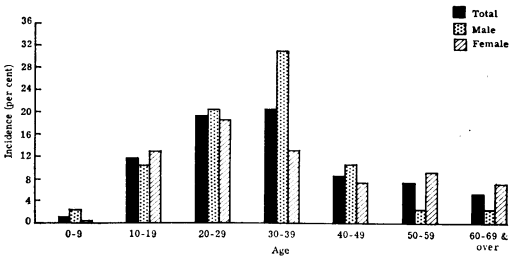

Fig 13 *Incidence of significant hæmagglutination antibody titre (>1:40) in relation to the age of patients with minor aphthous ulcers*

DISCUSSION

A clinical comparison of the three types of recurrent oral ulcers is shown in Table 4; histological and immunological differences are reported elsewhere (Lehner & Sagebiel 1966, Lehner 1967*a*, 1968*a*).

Comparison between Minor Aphthous Ulcers and Major Aphthous Ulcers

The proportion of females to males is higher in MiAU (56%) than MjAU (44%). The peak age of attendance is higher in MjAU (30–39 years) than in MiAU (20–29 years), although the peak incidence of the age of onset is the same (10–19 years). The total duration of ulceration is significantly longer and the severity greater in MjAU than MiAU. Recurrences are significantly more frequent and ulcers persist longer in MjAU than in MiAU. Moreover, ulcers are significantly larger, greater in number and scarring is much more common in MjAU than MiAU. The other important difference between the two groups is the frequent involvement of the pharynx and palate in MjAU. From careful assessment of patients' histories, it seems that MiAU may occasionally change after many years into MjAU and vice versa, although objective evidence for this transition is at present lacking.

Histological and electron microscopical examination failed to show any difference between the two varieties of ulcers. The histological criteria for delayed hypersensitivity, as laid down by Coe *et al.* (1966) are fulfilled and the incidence of focal sialadenitis is similar (Lehner 1968*a*).

Humoral and cell-bound antibodies are found in both conditions. They show a raised incidence of hæmagglutinating, complement-fixing and precipitating antibodies and immunoglobulin binding is found in autologous tissue. Oral mucosa stimulates lymphocyte transformation in both lesions but skin only in MjAU (Lehner 1967*b*). Serum immunoglobulin estimations show raised IgG and IgA in both lesions, but only those in MjAU reach statistical significance. IgG and IgA remain within normal limits in the saliva of both conditions (Lehner 1968*b*).

The major differences between MiAU and MjAU can be ascribed to the greater severity of the latter because the ulcers last longer, they are more severe, larger in size and number and they recur more frequently.

Comparison between Minor Aphthous Ulcers and Herpetiform Ulcers

The proportion of female patients is greater in HU (73%) than in MiAU (57%). The peak age of attendance and onset of ulceration is 10 years higher in HU than in MiAU. Duration of ulceration does not show a difference but HU are significantly more severe and a greater proportion recur more frequently and produce scars than in MiAU. HU are initially significantly smaller, present in crops and are greater in number than MiAU. The site of ulceration is restricted in MiAU predominantly to the lips, cheeks and sides of the tongue, but HU are found in addition on the dorsum of the tongue, palate, pharynx, floor and gum.

Therapeutic response to local tetracycline is usually dramatic in HU but much less marked in MiAU, while corticosteroids show a good response in MiAU but poor results in HU.

Microscopically, the striking difference is the presence of intranuclear inclusion bodies and epithelial vesicles in HU (Lehner & Sagebiel 1966).

The immunological findings show important differences between the two conditions. The incidence of antibodies is significantly raised in MiAU but not in HU and immunoglobulin binding is not found in HU. Whilst lymphocyte transformation is stimulated with oral mucosa in a very significant proportion of MiAU ($P<0{\cdot}001$), this occurs less commonly in HU ($P<0{\cdot}05$). However, muscle-stimulated lymphocyte transformation is seen exclusively in HU. Serum and salivary immunoglobulins are statistically within normal limits in both conditions, but IgA clearance is significantly depressed and serum IgA is slightly raised in HU.

It is evident that sufficiently important clinical pathological and immunological differences are found between aphthous and herpetiform ulcers to justify their seggregation into two separate diseases.

The similarity in clinical appearance between herpetiform ulcers and herpes simplex lesions, the presence of epithelial vesicles and intranuclear inclusion bodies and the absence of significant antibodies to oral mucosa are consistent with a viral ætiology of HU.

Behçet's Syndrome

Oral manifestations in Behçet's syndrome are indistinguishable from the focal oral ulcers, except for the raised incidence of herpetiform ulcers. Oral ulcers in Behçet's syndrome display all the variations of the three types of focal ulcers. This analysis offers support for Touraine's concept (1941, 1955) that RAU are part of a wider condition named 'aphthosis'.

Correlation of Antibodies with Clinical Features

The incidence or titre of humoral antibodies was not related to the age, sex, duration or severity of MiAU. Humoral antibodies were not correlated with ulcer remissions and exacerbations and therefore their exclusive role in the pathogenesis of these ulcers is doubtful. This is in contrast to the behaviour of cell-bound antibodies, as assessed by lymphocyte transformation, which is absent or diminished in a remission and increased in an exacerbation of ulceration (Lehner 1967*b*). These observations suggest that lymphocytes play some part in the pathogenesis of recurrent aphthous ulcers and this appears to be corroborated by the histological and electron-microscopical observations.

As direct tests for cytotoxicity of oral mucosa by the humoral or cell-bound antibodies have not been carried out, the part that these antibodies may play independently or together cannot be assessed. The autoimmune hypothesis postulated for recurrent aphthous ulcers (Lehner 1967*c*) will depend on the outcome of direct tests for pathogenicity of antibodies to oral mucosa.

Summary

(1) Immune disorders of the mouth are broadly outlined, with emphasis on autoimmunity and the criteria for its recognition.

(2) Significant clinical differences are found between minor aphthous ulcers, major aphthous ulcers and herpetiform ulcers in terms of size, number, frequency of recurrence, severity, scarring and site of ulceration.

(3) Minor aphthous ulcers and major aphthous ulcers are two varieties of the same condition and differ predominantly in the degree of severity of ulceration.

(4) Herpetiform ulcers show distinctive clinical, pathological and immunological features which are consistent with a viral ætiology.

(5) Behçet's syndrome can present with any one of the three types of focal ulcers and the diagnosis can be established only by the associated extraoral manifestations.

(6) The incidence and titre of hæmagglutination antibodies are not related to the age or sex of the patient, nor to the duration or severity of recurrent aphthous ulcers.

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REFERENCES
Beutner E H & Jordon R E
(1964) *Proc. Soc. exp. Biol. (N. Y.)* **117**, 505
Beutner E H, Witebsky E, Ricken D & Adler R H
(1962) *J. Amer. med. Ass.* **182**, 156
Bunim J J (1961) *Ann. rheum. Dis.* **20**, 1
Coe J E, Feldman J D & Lee S
(1966) *J. exp. Med.* **123**, 267
Cooke B E D
(1960) *Brit. dent. J.* **109**, 83
(1961) *Dent. Pract it. dent. Rec.* **12**, 119
Farmer E D (1958) *Dent. Pract it. dent. Rec.* **8**, 177
Glynn L E & Holborow E J
(1965) Autoimmunity and Disease. Oxford
Lehner T
(1964) *Lancet* ii, 1154
(1967*a*) *Brit. med. J.* i, 113
(1967*b*) *Immunology* **13**, 159
(1967*c*) *Brit. dent. J.* **122**, 15
(1968*a*) (In preparation)
(1968*b*) (In preparation)
Lehner T & Sagebiel R W
(1966) *Brit. dent. J.* **121**, 454
Mackay I R & Burnet M F
(1963) Autoimmune Diseases. Springfield, Ill.
Ship I I, Morris A L, Durocher R T & Burket L W
(1960) *Oral Surg.* **13**, 1191
Sircus W, Church R & Kelleher J
(1957) *Quart. J. Med.* **26**, 235
Touraine A
(1941) *Bull. Soc. franç. Derm. Syph.* **48**, 61
(1955) *Presse méd.* **63**, 1493
Truelove S C & Morris-Owen R M
(1958) *Brit. med. J.* i, 603
Witebsky E (1959) In: Immunopathology. Ed. P Grabar & P Miescher. Basel; p 1

The following paper was also read:

The Field-Marshal's Dentures: Interesting Details of Construction of the Dentures of the Great Duke of Wellington KG (1769–1852)
Mr C Bowdler Henry

The dentures consisted of two full sets in gold and ivory, the upper and lower plates in each set being joined by springs and the front teeth in both sets being human teeth. The paper was illustrated with colour slides and radiographs. (By permission of the Duke of Wellington KG.)

Meeting October 23 1967

Professor John Boyes (*School of Dental Surgery, Edinburgh*) delivered his Presidential Address entitled **Palatal Tumours.**